

Department of Molecular Medicine and Surgery
Lower Gastrointestinal Research Group
Karolinska Institutet
Stockholm, Sweden

EARLY RECTAL CANCER AND SCREENING FOR COLORECTAL CANCER

Deborah Saraste



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*”Ja, livet är riskabelt nog min prins
-törhända det riskablaste som finns.
Men står man bara stark och håller ut
får också denna farlighet sitt slut!”*

Lennart Hellsing ur ”Fem prinsar”

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PAPERS I-IV

ABSTRACT

Colorectal cancer (CRC) is the second most common form of cancer in Europe, and population based screening for colorectal cancer is recommended by the European Union. Screening enables detection of precursor lesions, *i.e.* adenomas, and cancer at an early stage, and randomised trials have demonstrated that screening reduces mortality in colorectal cancer. In rectal cancer, oncological results after abdominal resection surgery have improved over many years, but the morbidity, mortality and negative functional side effects following surgery and oncological treatment are considerable. Local excision techniques, on the other hand, demonstrate excellent functional results and a low morbidity and mortality but have high local recurrence rates, mainly since the technique does not allow for excision of mesorectal lymph nodes, which could be exposed to metastatic disease not detectable in the preoperative radiological staging. Since further expansion of population based screening programs for CRC will increase the detection of early cancer, local excision techniques are of great interest, provided that an adequate oncological outcome can be ensured.

In **paper I** all patients in Sweden undergoing surgery for stage I rectal cancer 1995-2006 were assessed regarding survival, local recurrence rates and risk factors for death. Patients undergoing local excision had a higher local recurrence rate and a poor survival, especially in the age group ≥ 80 years, compared to patients undergoing abdominal resection surgery.

Paper II analysed risk factors for lymph node metastases in patients with rectal cancer. All patients in Sweden 2007-2010 with histopathologically confirmed radical resections of pT1-2 rectal cancer following abdominal resection surgery without (neo)adjuvant treatment were included. T2 stage, poor differentiation and vascular infiltration were identified as risk factors for lymph node metastases. A model calculating the total risk depending on the number of risk factors included, displayed a risk range of 6-65 % and 11-78 % in T1 and T2 tumours respectively.

In **paper III** all Swedish patients aged 60-69 years with screening detected colorectal cancer were compared to those with non-screening detected cancer diagnosed 2008-2012. Pre- and postoperative staging, MDT-assessment, surgical and oncological treatment were compared between the groups. Patients with screening detected cancer were staged and MDT-assessed to a higher extent compared to those with non-screening detected cancer and tumours were found at an earlier stage in the screening group. Surgical and oncological treatment did not differ between the groups. Patients with endoscopically resected cancer did not undergo staging and MDT-assessment to the same extent as did patients with surgically resected cancer.

Paper IV included all individuals with a positive FOBT in the Stockholm screening programme, January 2008 - June 2012. Complications and mortality within 30 days after interventions, *i.e.* colonoscopies or surgery for adenomas or cancer, subsequent to a positive screening test were assessed. Total complication rates were acceptable and mortality was low, but the rate of anastomotic leakage, which was 13 % and 12 % in the adenoma and cancer surgery groups respectively, was higher than expected.

LIST OF SCIENTIFIC PAPERS

- I. Local excision in early rectal cancer- outcome worse than expected: A population based study**
D. Saraste, U. Gunnarsson, M. Janson
European Journal of Surgical Oncology
2013; 39: 634-639

- II. Predicting lymph node metastases in early rectal cancer**
D. Saraste, U. Gunnarsson, M. Janson
European Journal of Cancer
2013; 49: 1104-1108

- III. Differences in pre-therapeutic work up and treatment in patients with screening vs. non-screening detected colorectal cancer**
D. Saraste, A. Martling, PJ. Nilsson, J. Blom, S. Törnberg, M. Janson
Submitted for publication

- IV. Complications and mortality after colonoscopy and surgery for colorectal cancer screening-detected adenomas and cancer**
D. Saraste, A. Martling, PJ. Nilsson, J. Blom, S. Törnberg, R. Hultcrantz, M. Janson
Manuscript

THESIS AT A GLANCE

	Paper I	Paper II	Paper III	Paper IV
Aim	Comparison of long-term survival in patients with stage I rectal cancer after local excision vs. abdominal resection surgery.	Assessment of risk factors for lymph node metastases in T1 and T2 rectal cancer.	Comparison of patients with screening detected vs. non-screening detected CRC regarding staging, MDT-assessment and treatment.	Assessment of complications and mortality after colonoscopy and surgery following a positive FOBT in screening individuals.
Patients	All patients in Sweden undergoing surgery for stage I rectal cancer, 1995-2006.	All patients in Sweden undergoing abdominal surgery for rectal cancer, 2007-2010, without (neo)adjuvant treatment. p T1-2 tumours included.	All patients in Sweden, 60-69 years old, with screening and non-screening detected CRC, 2008-2012.	All patients in the Stockholm/Gotland screening programme with a positive FOBT January 2008 - June 2012.
Methods	5-year survival and HR for mortality within 5 years after surgery.	Multivariate logistic regression analyses of the risk of lymph node metastases.	Comparison of differences between the groups	Assessment of 30-day mortality and complication rates.
Results	<p>5-year relative survival: anterior resection, 0.95 (0.92-0.97), local excision 0.81 (0.75-0.88).</p> <p>Risk factors for 5-year mortality in patients ≥ 80 years:</p> <p>Local excision, <i>HR</i>= 1.55 (1.17-2.05), male gender <i>HR</i>= 1.59 (1.27-1.99) and age <i>HR</i>= 1.07 (1.04-1.11).</p>	<p>T2 tumour stage, <i>OR</i>= 1.97 (1.19-3.25), poor differentiation, <i>OR</i>= 6.47 (2.71-15.4), vascular infiltration, <i>OR</i>= 4.34 (2.46-7.65).</p>	<p>Staging of surgically resected tumour in screening (94 %) vs. non-screening (87 %) and of endoscopically resected tumour in screening (46 %) vs. non-screening (24 %) groups. Corresponding numbers for MDT assessment were 90 %, 69 %, 25 % and 16 % respectively.</p>	<p>Rates of post-polypectomy bleeding 14/1000 and perforation 2.5/1000. Complication and anastomotic leakage rates after adenoma surgery were 27 % and 13 % respectively and after cancer surgery, 50 % and 12 % respectively.</p>
Conclusion	The 5-year survival was poor after local excision surgery, especially in patients ≥ 80 years.	T2 tumour stage, poor differentiation and vascular infiltration were risk factors for lymph node metastases.	Patients with screening detected CRC were extensively staged and MDT assessed, but this was not the case for patients with endoscopically resected CRC.	Overall complication rates and mortality were acceptable. Anastomotic leakage rates were higher than expected.

LIST OF ABBREVIATIONS

ACG	American College of Gastroenterology
AJCC	American Joint Committee for Cancer
APE	Abdominoperineal excision
AR	Anterior resection
ASA	American Society of Anesthesiologists physical status classification
cCR	Clinical complete response
CME	Complete mesocolic excision
CRC	Colorectal cancer
CRM	Circumferential resection margin
CRT	Chemoradiotherapy
CT	Computed tomography
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
EUS	Endoluminal ultrasonography
FIT	Faecal immunochemical test
gFOBT	Guaiac-based faecal occult blood test
Gy	Gray
HR	Hazard ratio
ICD-10	International Classification of Diseases
IPR	Inpatient registry
LE	Local excision
MDT	Multidisciplinary team conference
MRI	Magnetic resonance imaging
OR	Odds ratio
pCR	Pathological complete response
SCRCR	Swedish Colorectal Cancer Registry
TA	Transanal
TEMS	Transanal endoscopic microsurgery
TME	Total mesorectal excision
TNM	Tumour Node Metastasis staging system
UICC	Union for International Cancer Control

BACKGROUND

Colorectal cancer

Epidemiology

Of estimated 3.5 million new cases of cancer in Europe every year, colorectal cancer (CRC) is the second most common form of cancer with 447.000 new cases, and the second most common cause of death from cancer with 215.000 deaths per year ¹. In Sweden, the incidence is 6000 cases per year, of which 2/3 are originating from the colon, and 1/3 from the rectum. The number of cases has increased with 70 % over the past 40 years. This is mainly due to the successively aging population, since the increase in age standardized incidence is not as pronounced. Overall mortality is slightly decreasing. The overall 5-year survival in CRC is around 50 %, but survival is clearly stage dependent. Swedish national population based data on 5-year relative survival is shown below ^{2,3}.

Table 1. Relative survival in CRC, Sweden 2007-2013.

Relative survival, 2007-2013	Rectal cancer	Colon cancer (elective sur- gery)
Stage I	93 %	98 %
Stage II	82 %	93 %
Stage III	68 %	74 %
Stage IV	12 %	26 %

Staging

Staging of CRC is made according to the TNM staging system which classifies colorectal cancer according to the growth of the primary tumour (T), the regional lymph-node status (N) and distant metastases (M). Staging is made through physical examination, rectoscopy/endoscopy, imaging, surgical exploration and histopathological examination. The Union for International Cancer Control (UICC) and the American Joint Committee for Cancer (AJCC) collaborates in maintenance and revision of the system. Since Jan 1, 2010 the 7th edition of the TNM staging system is at use in Sweden.

Table 2. Tumour staging according to the TNM Classification of Malignant tumours

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Invasion of submucosa
T2	Invasion of muscularis propria
T3	Invasion through muscularis propria into subserosa or non-peritonealised pericolic or perirectal tissue
T3a	Tumour extends <1 mm beyond muscularis propria
T3b	Tumour extends 1-5 mm beyond muscularis propria
T3c	Tumour extends 5-15 mm beyond muscularis propria
T3d	Tumour extends >15 mm beyond muscularis propria
T4a	Invasion through visceral peritoneum
T4b	Direct invasion of other organs or structures
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in 1-3 regional lymph nodes
N1a	Metastases in one regional lymph node
N1b	Metastases in 2-3 regional lymph nodes
N1c	Tumour deposits in subserosa or non-peritonealised pericolic or perirectal tissues without regional lymph node metastases
N2	Metastases in 4 or more regional lymph nodes
N2a	Metastases in 4-6 regional lymph nodes
N2b	Metastases in 7 or more regional lymph nodes
MX	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases
M1a	Metastases confined to one organ/site (including non-regional lymph nodes)
M1b	Metastases in more than one organ/site or peritoneum

Adapted from TNM Classification of Malignant tumours, 7th Edition

Preoperative clinical staging (cTNM)

Colon

Complete endoscopic examination of the colon and rectum is advised including biopsies of any lesions requiring surgical treatment. Chest and abdominal computed tomography (CT) is used for staging of the primary tumour, the lymph node status and the distant metastases. For liver lesions in which CT is inconclusive, further investigations with contrast enhanced ultrasound or MRI can be added.

Rectum

Digital examination followed by a rigid rectoscopy with biopsies for histopathological diagnosis and assessment of the distance of the tumour to the anal verge and a colonoscopy for complete examination of the colon are included in the primary investigation. Chest and abdominal computed tomography is used for staging of distant metastases. Pelvic magnetic resonance imaging (MRI) is conducted in order to obtain information on the stage of the primary tumour, involvement of the mesorectal fascia, extramural vascular invasion, and staging of mesorectal and pelvic sidewall lymph nodes, thus identifying which patients will benefit from neoadjuvant treatment, and which should proceed to abdominal surgery or local excision without previous oncological treatment. Endoluminal ultrasonography (EUS) can be used in early rectal cancer in ad-

dition to MRI for assessment of T-stage. The extent of locally advanced CRC or/and metastatic disease can be determined by positron emission tomography/computed tomography (PET/CT) with 18F-FDG (2-deoxy-2-[fluorine-18]fluoro-D-glucose).

Preoperative staging is essential for the planning of further surgical and oncological treatment and the decision on whether curative or palliative intent is the aim of the treatment.

Table 3. Correlation between anatomical staging and prognostic groups

Stage	T	N	M
0	Tis	N0	M0
I	T1-T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

Adapted from the American Joint Committee on Cancer Staging Manual, 7th Edition

Accuracy of preoperative imaging

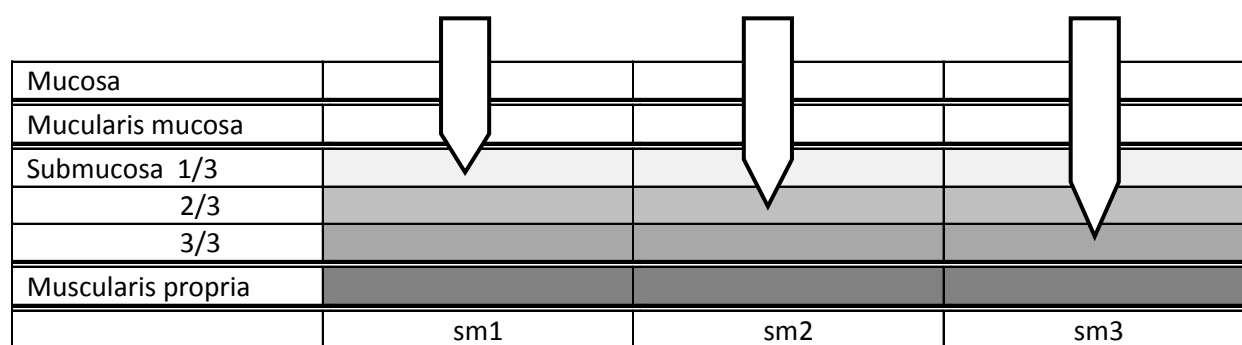
Results from the MERCURY-study shows that high-resolution MRI in preoperative staging of rectal cancer has a high specificity for predicting the depth of tumour invasion outside the muscularis propria (92.5 %) and a high specificity for negative mesorectal fascia involvement (92 %) when compared to histopathological assessment of the resected specimen as a reference standard ^{4,5}. However, meta-analyses have demonstrated the specificity on MRI regarding lymph nodes assessment is poor (71%) ⁶. EUS, CT and MRI in rectal cancer displays equally poor results regarding the specificity (78 %, 74 % and 76 % for EUS, CT and MRI respectively) for correct staging of lymph node involvement in rectal cancer. Regarding invasion of the muscularis propria, EUS and MRI have a similar sensitivity (94 %), but EUS has a higher specificity (86 %) compared to MRI (69 %) ⁷. In staging of colon cancer pooled data from meta-analyses have demonstrated a sensitivity and specificity for detection of tumour invasion (T-stage) to 86 % and 78 % respectively, with corresponding values for identification lymph node status of 70 % and 78 % respectively ⁸. Hence the preoperative assessment of lymph node metastases remains a challenge, which also has impact on the decision making and oncological outcome in case of local excision surgery.

Histopathological staging (pTNM)

The histopathology report is based on the TNM staging system and the WHO Classification of Tumours of the Digestive System ⁹. Since 2010 the 7th edition of TNM system is uniformly

used for histopathology reporting in Sweden. More than > 90 % of CRC are adenocarcinomas originating from epithelial cells of the colorectal mucosa (other colorectal cancer types are neuroendocrine, squamous cell, adenosquamous, spindle cell and undifferentiated carcinomas). Only adenocarcinomas are reported to the Swedish Colorectal Cancer Registry. The criterion of carcinoma is infiltration of the tumour through the muscularis mucosae. Previously the terminology of poorly, moderately and highly differentiated cancer has been used. However, according to the WHO 2010 classification, the use of the terms high and low grade cancer is advocated. Grading of the cancer into low grade and high grade cancer is based on the glandular formation, where $\geq 50\%$ equals low grade cancer and $< 50\%$ equals high grade cancer. A low grade cancer thus corresponds to a highly differentiated cancer. The presence of a mucinous cancer is noted, defined as $\geq 50\%$ of the tumour volume being composed of extracellular mucin. In addition to the TNM system, the pathology report will include information on the subclassification of T1 tumours according to the Kudo classification (later modified by Kikuchi), which divides the submucosa into thirds, sm1, sm2 and sm3^{10,11}. However, this subclassification cannot be accomplished if the muscularis propria is not represented in the specimen.

Figure 1. Submucosal tumour invasion, sm1-3



Adapted from Kudo et al., Endoscopy 1993;25:455-61

Cancer growth in pedunculated polyps are classified according to the Haggitt-classification I-IV¹². Haggitt level I-III corresponds to T1sm1 in the Kikuchi classification, whereas Haggitt level IV corresponds to the submucosal invasion of T1sm1-3.

Table 4. Haggitt classification of T1 cancer in pedunculated polyps

Haggitt-classification	Invasion to
1	Head of polyp
2	Neck of polyp
3	Stalk of polyp
4	Submucosa of underlying colonic wall

Adapted from Haggitt et al., Gastroenterology 1985;89:328-36

The number of examined and positive lymph nodes and the presence of perineural growth, small-vessel lympho-vascular growth or extramural venous invasion are noted in the histopathology report, as are the minimum circumferential and longitudinal resection margins and if these are microscopically free of tumour. In case of neo-adjuvant therapy the tumour regression grade (0-3) is noted.

Studies have demonstrated that an increasing number of examined lymph nodes after resection surgery in colon cancer is associated with increased survival in stage II and III cancer¹³. The reasons for this are partly that a larger number of examined nodes decreases the risk of understaging, but also that increased focus on and awareness of the importance of histopathology in the treatment of colorectal cancer has improved the quality of the histopathological assessment¹⁴. Detection and examination of at least 12 lymph nodes is considered a quality indicator of both the surgical resection and the histopathological examination¹⁵.

The issue of tumour deposits needs some extra attention. In previous versions of the TNM manual, tumour deposits were classified as either as discontinuous extension (T3) or as positive nodes depending on size and shape. To avoid misclassification of the N-stage, consequently affecting adjuvant treatment and survival, tumour deposits are now classified as N1c in absence of other positive nodes. According to TNM 7 tumour deposits “represent discontinuous spread, venous invasion with extravascular spread (V1/2) or a totally replaced lymph node (N1/2). If such deposits are observed with lesions that would otherwise be classified as T1 or T2, then the T classification is not changed, but the nodule(s) is recorded as N1c. If a nodule is considered by the pathologist to be a totally replaced lymph node...it should be recorded as a positive lymph node”.

Multidisciplinary team conferences (MDT)

In multimodal contemporary treatment of patients with colorectal cancer, the involvement and special competences of different specialities are necessary. Not only staging and planning of surgery, but also timing, sequencing and strategy concerning neo-adjuvant and adjuvant treatment in relation to surgery is needed to optimise treatment for the individual patient. The physical and mental status and wishes of the individual patient are taken into account in addition to the characteristics of the tumour.

Colorectal surgeons, radiologists, pathologists, oncologists and specialised nurses participate in the team, and when needed, liver surgeons attend. Every individual patient is discussed pre- and postoperatively, and sometimes multiple assessments are necessary, depending on the complexity of the multimodal treatment.

In a systematic review Wright *et al.* concluded that MDT conferences (not only confined to colorectal cancer) resulted in positive patient outcomes in terms of diagnosis and/or treatment planning, patient survival and satisfaction, and clinician satisfaction in terms of communication and cooperation¹⁶. Specific studies on colorectal cancer have shown that patients with rectal cancer are more completely staged than patients with colon cancer, at least in stage IV disease¹⁷. Fewer cases of involved circumferential resection margins (CRM+) are seen among patients with rectal cancer who are discussed at MDT conferences¹⁸.

The Swedish board of Health and Welfare states that for patients with CRC, “the healthcare provider should always evaluate different treatment options...in a multidisciplinary conference”¹⁹. According to Swedish National quality data on patients undergoing elective surgery (polypectomies excluded), 83 % and 96 % of patients with colon and rectal cancer respectively are assessed at a preoperative MDT-conference.

Surgical treatment of colorectal cancer

Colon cancer

The introduction of the Total mesorectal excision (TME)-technique in rectal cancer dramatically decreased local recurrence rates after surgery²⁰. In colon cancer surgery attempts to standardize the surgical resection technique came later, with the introduction of complete mesocolic excision (CME) for colon cancer as proposed by Hohenberger *et al.* in Erlangen. In analogy with the TME-technique in rectal cancer surgery, the CME technique is based on surgical dissection along embryological planes with sharp separation of the visceral and parietal tissue layer. Central ligation of supplying arteries relevant for the tumour affected segment is advocated and lymph node yield is thus maximized along with an intact embryological envelope around the specimen²¹. In the Erlangen-material, the 5-year cancer-specific survival rate was 89 % in patients undergoing curative resections in stage I-III tumours. The local recurrence rate by the end of the study period (1978-2002) was 3.6 %. However, the optimal extent of the mesocolic resection and central vascular ligation and how this affects long term oncological results outside a single centre is not clear. Meta-analyses of CME surgery demonstrates that CME surgery removes more tissue around the tumour and harvests more lymph nodes, but data are sparse regarding the long term survival benefit compared to traditional radical resection of the colon²². However, a recent study by Bertelsen *et al.* comparing CME to conventional colon cancer surgery, concluded that disease-free survival was higher after CME, in all included stages (I-III) with a 4-year survival of 86 % compared to 73 % ($p = 0.0014$) after CME and non-CME surgery respectively²³.

Laparoscopic resections in colon cancer

Large randomized multi-institutional trials have shown that long-term oncologic results in terms of disease-free and overall 5-year survival, and overall recurrence rates are similar comparing laparoscopic and open resections for colon cancer²⁴. Short term oncologic results such as positive resection margins, number of lymph nodes removed and morbidity and mortality are also comparable²⁵.

Rectal cancer

Total mesorectal excision (TME)

The modern era of rectal cancer surgery began with the introduction of the Total mesorectal excision (TME)-concept as proposed by Bill Heald in 1982²⁰. Opposite to the blunt resection technique previously used, the surgical dissection introduced by Bill Heald is sharp and under direct vision, and includes a complete excision of the mesorectum along the embryological avascular planes between the mesorectum and the autonomic nerve plexae and pelvic fascia. The inferior mesenteric artery is ligated in proximity to the aorta to ensure resection of lymph nodes relevant for drainage of the tumour. With this approach 5-year local recurrence rates of 3.7 % and 5-year survival of 87 % in patients with Dukes stage A-C were reached after surgery without neoadjuvant or adjuvant treatment, which at the time was astonishing results compared to previous recurrence rates of 40 %²⁶. Corresponding survival and local recurrence rates in national Swedish population based data shows a 3-year relative survival of 90 % in patients

with stage I-III disease (equals Dukes stage A-C) after resection surgery (2007-2013) and cumulative 5-year local recurrence rates of 7 % (1995-2008) in patients with stage I-IV disease, including patients with and without neoadjuvant radiotherapy ³.

Anterior resection (AR)

The dissection is performed according to the principles of TME-surgery. A distal resection margin of 1 cm is generally accepted in low-lying tumours to promote sphincter-preserving surgery instead of abdominoperineal excision, and in patients receiving pre- or postoperative radiotherapy a margin even less than 1 cm is discussed ²⁷. In more proximal tumours, the mesorectal excision is partial since the complete mesorectum is not excised down to the pelvic floor, and a resection margin of 4-5 cm is advocated to include sufficient mesorectal tissue in the specimen. Short term morbidity and long term oncological results are comparable in TME and partial mesorectal excision (PME) ²⁸.

The anastomosis can in high tumours or in cases of a colo-anal anastomosis be hand sewn, but is otherwise created with a circular stapling device. A side-to-end anastomosis or J-pouch is advocated in low lying tumours, in order to improve functional results ^{29,30}.

Abdominoperineal excision (APE)

To ensure an adequate distal resection margin in low lying tumours, or in case a poor functional outcome is expected with an anastomosis, or if numerous risk factors for anastomotic leakage are present, APE is performed.

While oncological results improved in AR after the introduction of the TME-technique, no such effect was observed in APE. In the classical APE the dissection follows the levator muscles to the sphincter complex, hereby creating a “waist” of the specimen. The proximity to the sphincter complex in the “waist” increases the risk of CRM involvement and tumour perforation and thus increases the risk of local recurrence and impaired survival in patients operated with APE compared to AR ³¹. In order to improve these results the Extralevator APE (ELAPE) was introduced. The procedure allows mobilization of the mesorectum, only until the proximal origin of the levator muscle, after which a stoma is formed and the abdomen is closed. The perineal phase of the operation is performed with the patient in preferably prone position to improve visualisation. The sphincter complex and the levator muscles are included in the resection. To further improve visualization the coccyx can be removed. This technique eliminates the “waist” of the specimen, and results in a cylindrical specimen, thereby reducing resection margin involvement from 41 % to 15 % and intraoperative perforations from 23 % to 4 % compared to the conventional APE, as demonstrated by surgeons in Stockholm and Leeds after the introduction of ELAPE ³². A meta-analysis from 2014 comparing ELAPE to conventional APE confirmed these results demonstrating a significant reduction in the rate of involved resection margins, intraoperative perforations and local recurrence rates in favour of ELAPE ³³.

Further modification of this concept into intersphincteric APE, ELAPE and ischioanal APE has been proposed to meet the different indications for APE ³⁴.

Hartmann's procedure

In patients with high comorbidity or with a poor sphincter function Hartmann's procedure could be considered as an alternative to AR or intersphincteric resection. The dissection follows the same principles as for AR, but instead of an anastomosis, a sigmoidostomy is created, and the rectal stump is closed.

Laparoscopic and robotic surgery

Laparoscopic and robotic surgery for rectal cancer is increasingly gaining ground as an alternative to open surgery. A Cochrane report was undertaken 2014 to evaluate differences in short- and long-term outcomes, comparing laparoscopic versus open total mesorectal excision for rectal cancer. Results regarding five-year disease-free survival, local recurrence rates and overall survival were similar between the laparoscopic and open TME groups, as were the number of resected lymph nodes and the surgical resection margins. No difference was seen between the groups regarding 30-day morbidity. Similar anastomotic leakage rates were demonstrated (7.7 % vs. 6.3 %; laparoscopic vs. open), however fewer wound infections and less postoperative bleeding was seen in the laparoscopic group. No differences were demonstrated in quality of life regarding functional recovery, bladder and sexual function. In the laparoscopic group length of stay was reduced by two days and time to first defecation was shorter, but costs were higher for laparoscopic surgery³⁵.

With robotic surgery in rectal cancer, similar long term oncological results in terms of 5-year overall survival, disease free survival and local recurrence rates have been demonstrated compared to laparoscopic surgery. No benefits have been observed compared to laparoscopic surgery but the cost is increased³⁶. Previous studies of short term outcome have displayed a longer operation time in the robotic group, but otherwise similar results regarding overall major complications and quality of the resected specimen in terms of distal and circumferential resection margins and harvested lymph nodes³⁷.

Complications, morbidity and mortality after colorectal cancer surgery

Total complication rates of up to 50 % have been reported after rectal cancer surgery³⁸.

A recent meta-analysis including all prospective studies on surgery with AR and APE for rectal cancer, 1990-2008, demonstrated an anastomotic leakage rate of 11 % and a pelvic sepsis (defined as either anastomotic leak or pelvic abscess) rate of 12 %. Postoperative mortality was 2 %³⁹. After APE, perineal wound complications are a common problem. A multicenter study by West *et al.*, 2010, reported an overall wound complication rate of 38 % and 20 % after extra-levator- and standard APE respectively⁴⁰.

Complication rates after surgery for colon cancer are generally lower compared to rectal cancer surgery, but total complication rates of 20-33 % and anastomotic leakage rates of 3 % after open surgery for colon cancer are reported^{41,42}. Anastomotic leakage is a serious complication with an in-hospital mortality of 19 % compared to 3 % in patients without leakage after colon cancer surgery, and a decreased 5-year over-all and disease free survival⁴³.

Functional aspects

Sexual, urinary- and bowel function are all affected by rectal cancer surgery and the pelvic dissection itself, and can be further impaired by preoperative (chemo) radiotherapy.

Low anterior resection syndrome (LARS)

LARS is a condition characterised by incontinence, urgency, fragmented stool and frequent bowel movements after anterior resection surgery. With a validated scoring system for evaluation of the presence and severity of LARS, a Danish study included all patients who underwent curative resection for rectal cancer in Denmark 2001-2007. Major symptoms of LARS were observed in 41 % of the patients. Risk factors associated with major LARS were neoadjuvant therapy (short- or long-course radiotherapy or chemoradiotherapy), anastomotic leakage, age ≤ 64 years at surgery, and female gender. The odds of LARS were higher for long-course chemo-radiotherapy vs. short-course radiotherapy and for TME vs. PME⁴⁴.

Sexual and urinary dysfunction

Sexual dysfunction after rectal cancer surgery is common both in women and men, affecting their quality of life. A questionnaire-based study on 81 women and 99 men who had undergone APE, AR or transanal excision reported that 32 % of women and 50 % of men were sexually active after surgery, compared to 61 % and 91 % respectively before surgery ($p < 0.04$). Both genders reported a negative body image. Twenty-nine percent of the women, and 45 % of the men reported that surgery had made their sexual lives worse. More than 80 % of the patients reported that their ostomy caused a negative change in their sexual life⁴⁵.

Urinary dysfunction is a common problem after rectal cancer surgery. Comparing the outcome after ELAPE and APE, 46 % of patients experienced erectile dysfunction and 46 % urinary dysfunction after ELAPE. The corresponding rates after APE were 33 % and 17 % respectively⁴⁶.

Stoma

Ostomies are associated with a number of possible complications such as prolapse, retraction, stenosis, parastomal hernias and problems for the patient to handle the stoma in practical and psychological terms. Wound infections after creation of diverting loop ileostomies and loop-colostomies are reported in 3 % and 5-20 % respectively and dehydration is a common cause of postoperative morbidity in patients with loop-ileostomies, affecting up to 30 % of the patients^{47,48}. Furthermore loop-ileostomy closure is associated with a morbidity and mortality of 17 % and 0.4 % respectively⁴⁷. Nevertheless, to reduce the sequel of an anastomotic leakage, a defunctioning stoma after anterior resection of low rectal cancers is advocated. A multicentre randomized trial comparing patients undergoing low anterior resection for rectal cancer with or without a defunctioning stoma showed a difference in symptomatic leakage rates of 10 % vs. 28 % in the stoma and non-stoma groups respectively⁴⁹. However, the same study showed that after a median follow up of 42 months, 14 % of those with a temporarily intended defunctioning stoma never had it reversed. Regarding quality of life in patients with a permanent colostomy after resection of a rectal cancer with APE or Hartmann's procedure, compared to patients undergoing anterior resection with no stoma, a recent Cochrane review could not draw any firm conclusions in favour of either group⁵⁰.

Local excision (LE) techniques in early rectal cancer

Transanal surgery

The possibility of transanal resection is restricted to tumours in the lower part of rectum. When used for resection of malignant lesions, studies have showed high local and overall recurrence rates, and impaired survival in T2 tumours compared to TME surgery^{51,52}. One of the explanations for this is the problem of positive resection margins. However, since the introduction of transanal endoscopic microsurgery, and the evolution of endoscopic resection techniques, the use of transanal resection has decreased.

Transanal endoscopic microsurgery (TEMS)

Technique

In the beginning of 1980s the TEMS instrument and technique was developed by Gerhard Buess⁵³. TEMS is a minimally invasive technique for local excision of rectal neoplasms. The instrument consists of a rigid rectoscope, 4 cm in diameter, through which carbon dioxide is insufflated, and instruments are inserted. Pneumorectum is established and the operating field is visualized with magnification, either thorough a stereoscope or via connection to a laparoscopic video stack. Different single port access systems have been introduced successively over the years, *e.g.* Trans Anal Minimally Invasive Surgery (TAMIS), in which the basic concept of establishing transanal access to the rectum and creating a pneumorectum is the same as in TEMS, but where the devices and their limitations differ. However, TEMS is so far the more established technique.

An important limitation of TEMS and all other local excision techniques is the inability to excise the lymph nodes of the mesorectum. Possible lymph node metastases will therefore not be removed nor diagnosed, and hence there is a risk of recurrence and/or under-staging, which is one contributing cause of the questioned oncological safety.

Morbidity and mortality

After the TEMS procedure postoperative transient urinary retention has been reported⁵⁴. No long term effects on urgency or continence or quality of life have been observed⁵⁵. Multicenter data have shown an overall complication rate of 15 % and a mortality of 1 %⁵⁶. The rate of intraoperative peritoneal perforations is 5.8 %, which in 11 % of cases necessitated conversion to laparoscopic or abdominal resection surgery in a series of patients undergoing of TEMS resections of benign and malignant lesions⁵⁷. The hospital stay and operation time is shorter and the risk of postoperative complications is smaller ($p < 0.0001$) in TEMS compared to abdominal resection surgery for patients with T1 and T2 cancers⁵⁸.

As opposed to APE all local excision techniques enables the resection of early distal rectal cancers without the need of a permanent stoma.

Endoscopic resections

The technical development and performer skills in the area of endoscopic resection are under rapid progress. Until recently endoscopic mucosal resection (EMR) was the option for endoscopic removal of, predominantly, benign lesions. A limitation of this technique is the inability to resect lesions > 20 mm en-bloc, leading to a high rate of local recurrence. With the introduction endoscopic submucosal dissection (ESD) meta-analyses have demonstrated a higher radical resection rates (88 %) with acceptable complication rates (1 % of the complications necessitated surgical intervention), making ESD evolve as a possible option for local resection of CRC in addition to benign lesions⁵⁹. ESD was originally developed for early gastric cancer and the application on colorectal lesions has been more technically demanding with a higher risk of perforation. The ESD technique uses several different knives as cutting devices and removes a lesion in three steps: 1) injection of fluid into the submucosa to elevate the lesion from the muscular layer, 2) pre-cut of the surrounding mucosa, 3) dissection of submucosal connective tissue beneath the lesion. Small studies have compared ESD to TEMS for resection of early rectal cancer regarding en-bloc and R0 resection rates and local recurrence rates. After follow-up until 3 years, no significant difference between the two methods was seen^{60,61}. However, the number of lesions extending into the submucosa, *i.e.* true colorectal cancers, was small, and a large proportion of these required additional surgery, making the issue of local recurrence in case of cancer difficult to assess.

Resection with ESD is possible in both colon and rectum, but the risk of perforation increases in the proximal colon and therefore the primary interest has been lesions in the rectum, where ESD could evolve to an alternative or complement to TEMS in benign, and possibly in malignant lesions. The location of the rectum, surrounded by perirectal fat and in part distal to the peritoneal reflection, enables full thickness resections of lesions in the rectal wall by local excision techniques. This is not convenient in the colon, where a full thickness resection would create a perforation into the peritoneal cavity. However, studies on porcine models indicate that endoscopic full thickness resections with or without laparoscopic assistance could evolve as an option in the future⁶².

Oncological results after local excision

The literature on oncologic outcome after TEMS is divergent, as are the opinions on the oncological safety of TEMS and local excision techniques in general, and to which extent TEMS should be used in CRC-surgery with curative intent. Some obscurity also exists in the literature regarding the concept of local excision, which can include both transanal excisions and TEMS as well as endoscopic resections. This makes it, in some studies, difficult to separate the results of each technique.

In a meta-analysis from 2011 comparing TEMS to abdominal resection surgery for T1 and T2 rectal cancer a higher overall all and local recurrence rate after TEMS compared to abdominal resection surgery was observed, partly due to positive resection margins, but no difference in 5-year survival was observed⁶³. Local recurrence rates are the very central problem regarding the oncologic safety of TEMS and local excision in general, due to the fact that possible meta-

static nodes cannot be resected along with the surgical specimen. Another problem, especially regarding transanal excision, has been the high rates of positive resection margins. However, compared to transanal excision TEMS has a lower rate of positive resection margins and a longer disease-free survival⁶³. Two large studies with data from the American National Cancer Database have looked at trends of LE over time in comparison to abdominal resection surgery in stage I rectal cancer. You *et al.* looked at patients diagnosed with rectal cancer 1989-2003, comparing local excision to “standard resection”, however not specifying local excision as TEMS or TA. The results showed a local recurrence rate of 12.5 % vs. 6.9 % in T1-tumours and 22.1 % vs. 15.1 % in T2 tumours after LE and standard resection respectively. No difference in overall survival with regards to type of surgery was seen. By the end of the study, in 2003, 44 % of the T1-tumours were resected with LE. In a later study, also from the American National Cancer database, with data on patients with stage I rectal cancer, by 2010, 55 % of patients with T1-T2 tumours were treated with LE⁶⁴.

For comparison to the study by You *et al.*, data on Swedish patients with stage I, *i.e.* both T1 and T2, rectal cancers, diagnosed 1995-2001, resected with local excision (including transanal resection, TEMS and polypectomies) demonstrated 5- year local recurrence rates of 7 % and a 5-year survival of 95 %. In this material 12 % of all patients with stage I disease underwent local excision (including TEM, transanal excision and endoscopic resection)⁶⁵. Compared to the American material, the Swedish data displays low local recurrence rates, since stage I includes both T1 and T2 tumours, but still a very restrictive use of local excision as a treatment strategy for rectal cancer.

The risk of lymph node metastases

The central problem of oncological safety after local excision in (colo)rectal cancer revolves around the inability of present imaging techniques to correctly predict lymph node metastases and the inability of the any local excision technique to resect these lymph nodes en bloc with the tumour. Because of this, many have tried to assess the risk of lymph node metastases in order to conclude which patients could safely be offered a local excision procedure instead of an abdominal resection.

Since long the extent of tumour invasion into the bowel wall is considered a risk factor for lymph node metastases. The risk is 3-4, 8-11, 23-24 % in sm1, sm2 and sm3 tumours respectively^{66,67}. The risk in T2 tumours is 26 %⁶⁸. In addition to tumour stage, a large number of risk factors have been analysed in different studies. Female gender, lymphatic invasion, venous invasion, high grade cancer, increasing tumour diameter and tumour in the lower third of the rectum are some of the risk factors which have been addressed and noted as risk factors in different studies^{67,69,70}. Two recent meta-analyses by Bosch *et al.* and Glasgow *et al.* have assessed factors predicting lymph node metastases in T1 and T1-T2 CRCs respectively^{71,72}. In both studies, lymphatic invasion was the strongest predictor of lymph node metastases (expressed as an OR 8.6 and RR 5.2 respectively). In addition to lymphatic invasion, tumour depth (T2 vs. T1, OR 2.6) and poor differentiation (OR 2.4) was reported as the other two strongest predictors in the study by Glasgow *et al.*, who also looked at a rectal cancer subset, where poor differentiation at

the invasive front (OR 6.1) and tumour budding (OR 5.8) were most predictive of lymph node metastases. There was an evident heterogeneity among the studies included in the meta-analysis, reflected by the fact that 42 histopathological features were analysed, but only 41 % of these were reported in > 2 studies. In the study by Bosch *et al.*, submucosal invasion > 1mm (RR 5.2), budding (RR 5.1) and poor histological differentiation (RR 4.8) were the strongest predictors of lymph node metastases, in addition to lymphatic invasion.

To make clinical use of this information some authors have tried to make a decision tool of their findings calculating the additive effect of multiple risk factors. One example is a study by Kobayashi *et al.*, where risk factors for lymph node metastases in patients with lower rectal cancer were assessed. The risk ranged from 1 % in male patients with well differentiated T1-tumours, to 37 % in female patients with non-well differentiated T2-tumors⁶⁸. The above mentioned meta-analyses and example highlights that stage per se is not the strongest determinant of lymph node metastases. A low risk T2 cancer can have a lower risk of lymph node metastases than a high risk T1 cancer. Many of the studies evaluating the risk of lymph node metastases selected a limited number of potential risk factors for analysis, and to get an overall view, in which these theoretical calculations can be translated into practical advice and guidelines on which patients who, with preserved oncological safety, can be recommended a local excision procedure, remains a challenge.

Oncological treatment of non-metastatic CRC

Neoadjuvant radiotherapy (RT)

In patients with rectal cancer preoperative short-course radiotherapy (RT) 5x5 Gray (Gy) have in randomised trials demonstrated reduced local recurrence rates with > 50% compared to surgery alone, whereas effects on survival benefits are more uncertain⁷³⁻⁷⁵. The timing of surgery in relation to the radiotherapy and the question on whether short- (5 Gy x 5 days) or long-course (1.8-2.0 Gy x 25-28 days) radiotherapy is more favourable is still under debate. Results from the Stockholm III- trial exploring this matter will soon be available. This 3-armed randomised trial is comparing 5 Gy x 5 with immediate surgery, 5 Gy x 5 or 2 Gy x 25 with delayed (4-8 weeks) surgery, with local recurrence as the primary outcome⁷⁶.

Neoadjuvant chemoradiotherapy (CRT)

In locally advanced rectal cancer, preoperative CRT is advocated. Compared to RT, CRT improves local control, time to treatment failure and cancer specific survival⁷⁷. The standard CRT regimen consists of long course radiotherapy with concomitant 5-fluorouracil (5-FU) given either as bolus with leucovorin (FLv), as a prolonged infusion or as oral capecitabine.

Based on the risk of local recurrence, different algorithms for neoadjuvant treatment of rectal cancer without distant metastases have been proposed. The current European Society for Medical oncology (ESMO) Guidelines for rectal cancer proposes a categorisation into four risk groups; Very early, Early (Good), Intermediate (Bad), Advanced (Ugly)⁷⁸.

Table 5. Treatment algorithm based on the risk of local recurrence in non-metastatic rectal cancer

Risk Group (cTNM)	Therapeutic options
Very Early: T1sm1N0, possibly sm2	Local excision (TEM). In case of poor prognostic signs; sm-stage ≥ 2 / poor differentiation/vascular invasion, immediate abdominal TME surgery is recommended
Early (Good): T1-T2, T3a(b)N0 (middle/high tumour), N1 (high tumour) MRF-, EMVI-	Direct TME. In case of poor prognostic signs; crm+/N2 postoperative CRT or CT is recommended.
Intermediate (Bad): very low T2, T3 (not T3a (b) in middle/high rectum), limited T4aN0 N+, EMVI+, MRF-	Preoperative short course RT (5x5 Gy) or CRT followed by TME within 10 days
Locally advanced (Ugly): T3-T4b, MRF+, lateral node+	Preoperative CRT followed by surgery within 6-8 weeks. Optional in patients unfit for CRT is RT (5x5 Gy) followed by surgery after 8 weeks.

MRF (meso rectal fascia), EMVI (extra mural vascular invasion), RT (radiotherapy), CRT (chemoradiotherapy).

Adapted from Glimelius et al., Ann Oncol 2013;24 Suppl 6:vi81-8

According to this algorithm a very low proportion of the “Very early” and “Early” group of patients with rectal cancer would be subject to neo-adjuvant treatment. However, national Swedish data 2007-2010 shows that in the group of patients undergoing abdominal resection surgery for very early and early tumours, 54 % receive preoperative RT and 2 % CRT⁷⁹. Thus it seems that our aim of reducing local recurrence rates is resulting in a possible overtreatment with (C)RT.

Adverse effects after neoadjuvant RT and CRT

Preoperative (C)RT has both short- and long-term side effects. Immediate toxicity and side effects include fatigue, nausea, diarrhoea, erythema and acute lumbosacral plexopathy.

In the Dutch TME study comparing 5 Gy x 5 and surgery vs. surgery alone for rectal cancer, toxicity effects were negligible and no difference in morbidity was seen. Overall postoperative complication rates was higher in the RT+ group (48 % vs. 41 %), mainly due to more perineal wound complications⁸⁰. Sexual functioning was impaired in both males and females in the RT+ group, with significantly decreased ejaculation and erection function among men receiving RT⁸¹. Effects on Leydig cell function have been reported in other studies, increasing the risk of testosterone deficiency in males following RT⁸². Questionnaire-results after The Swedish Rectal cancer trial showed that incontinence for loose stools, urgency and emptying difficulties were all more common after RT and 30 % of the patients in the RT group experienced an impairment of their social lives due to bowel dysfunction compared to 10 % in the surgery only group⁸³. Symptoms of LARS are impaired by short- and long course radiotherapy or chemoradiotherapy compared to surgery only⁴⁴. There is also an increased risk of gastrointestinal disorders, neurological problems, pelvic hip fractures and secondary malignancies after radiotherapy⁸⁴.

Adjuvant chemotherapy

Colon cancer

Adjuvant chemotherapy with 5-FU and oxaliplatin after resection surgery of the primary tumour reduces the risk of death with 3-5 % in stage II and 15-20 % in stage III disease⁸⁵. European guidelines state that, following surgery in stage III colon cancer, six months of combination therapy of oxaliplatin and 5 FU+ leucovorin or oxaliplatin and capecitabine is recommended⁸⁵. In stage II, adjuvant therapy is not routinely used. However, a division of stage II into high and low risk groups according to tumour – related risk factors should guide the decision of giving adjuvant chemotherapy, at least with 5-FU, to high-risk stage II patients, with at least one of the following risk factors: lymph node sampling < 12, poorly differentiated tumour, vascular or perineural invasion, pT4 stage, clinical presentation with occlusion or perforation⁸⁵.

Rectal cancer

Randomised trials exploring the effect of adjuvant chemotherapy in rectal cancer after preoperative CRT and surgery have demonstrated conflicting results regarding the benefit of overall survival and recurrence, and a meta-analysis by Bujko *et al.* concluded that there was no evidence to recommend adjuvant chemotherapy in patients who had already received neoadjuvant CRT⁸⁶. However in patients who have not received neoadjuvant treatment, postoperative CRT is, according European guidelines, recommended in case of a positive resection margin (CRM+), perforation in the tumour area or in cases of a high risk of local recurrence (\geq pT3b and/or N+)⁸⁵.

Complete response and organ preservation in early rectal cancer

Much questioned when published in 2004, Habr-Gama *et al.* presented observations on “complete response” after neoadjuvant therapy with CRT (50.4 Gy + FLv) in rectal cancer. Clinical complete response (cCR) is defined as the absence of any clinically detectable residual tumour after neoadjuvant therapy, and pathologic complete response (pCR) as the absence of viable tumour cells after histopathological examination of the resected specimen. In the Habr-Gama study clinical complete response was obtained in 27 % of the patients and examination was done 8 weeks after completed CRT. The 5-year overall and disease-free survival was 100 % and 92 % respectively in the group with complete response, and 10-year overall and disease-free survival was 100 % and 86 % respectively⁸⁷. However, the concept of complete response and a subsequent “wait-and-watch” policy (omission of surgery with follow-up) is now accepted and has increased the interest in possible multimodal treatment strategies aiming at organ preservation in early rectal cancer.

CRT is routinely used in advanced rectal cancer for downstaging of the tumour and mesorectal nodal metastases. Current ideas advocate that these effects could also be of use in early rectal cancer thereby reducing the rate of margin involvement and decreasing local recurrence rates after local excision. When combining neoadjuvant CRT and local excision, the tumour, even in case of complete response, could be removed, with the low morbidity and good functional results known from local excision techniques, but without the oncological drawbacks of these

techniques. Histopathological evaluation of the specimen would reveal both pCR and tumours with adverse features for which additional surgery should be considered. However, the adverse effect of CRT when used for early rectal cancer is an issue that needs further evaluation.

In 2012, Lezoche *et al.* presented results from a small (50 patients in each arm) randomised trial where patients with cT2N0M0 underwent long-course CRT (50.4 Gy + 5-FU) followed by either TEMS or TME-surgery with a median follow-up of 10 years. All patients underwent R0-resections and there was no statistically significant difference in cancer related or overall survival between the groups. Local recurrence rates were 8 % in the TEM group and 6 % in the TME group⁸⁸.

A number of ongoing trials are investigating the possibilities of combining (C)RT and LE in early rectal cancer. The ACOSOG Z6041 single arm multi-centre phase II American trial is investigating long-course CRT (50.4 Gy + Capecitabine + Oxaliplatin) + LE (either transanal excision or TEMS) with surgery 8 weeks after completed CRT in patients with cT2N0M0 rectal cancer. For the primary outcome which is 3-year disease-free survival, data are not yet available. Secondary endpoints have been analysed showing a 44 % complete pathologic response rate, a high rate (99 %) of negative resection margins, but a rather high toxicity after CRT (39 % of patients developed grade ≥ 3 complications). The accuracy of cCR (defined as complete disappearance of the tumour on proctologic examination) to predict pCR was evaluated, demonstrating a sensitivity and specificity 85 % and 67 % respectively⁸⁹.

In the ongoing CARTS study patients with cT1-3N0M0 tumours below 10 cm from the anal verge are included. Neoadjuvant CRT is given as 50 Gy + Capecitabine. The study is a non-randomised feasibility study and the primary outcome measure is the number of patients with complete response after CRT and TEM, performed 8-10 weeks after completion of CRT. Secondary outcomes will be local recurrence rates and quality of life⁹⁰.

The TREC study has a little different approach. The aim of this phase II study is to determine the feasibility of randomising patients with early (T1-2N0M0) rectal cancer to either radical TME surgery or short course preoperative RT (5 Gy x 5) with TEMS after 8-10 weeks⁹¹.

The results of these trials will be interesting since (C)RT is added to the potentially curative treatment of, at least, T1 tumours with TEMS alone. The neoadjuvant treatment can add benefits in terms of downstaging, less involved resection margins and decreased local recurrence rates. However, it will also add morbidity. If we were to adapt the new strategies of heavy pre-operative oncological treatment for early rectal cancer it would change the way we presently look upon the risk-benefit ratio of neoadjuvant treatment and could increase the risk of over-treatment in early rectal cancer.

Screening for colorectal cancer

Introduction

Screening implies testing for a disease in apparently healthy individuals with no symptoms of disease. The purpose in cancer screening is to detect tumours at an early stage or even as pre-

cancerous lesions, thereby reducing disease-specific mortality. In CRC screening, the detection of both cancer and adenomas are considered important since there is a common notion that adenomatous polyps are precursors of CRC, and that removal of these polyps will reduce the incidence and mortality in CRC⁹²⁻⁹⁴. However, potential negative side effects and risks of the screening procedure itself and of subsequent interventions have to be taken into account and have to be in balance with the benefits of screening.

Evidence-based background for CRC screening

Faecal screening tests

Guaiac based faecal occult blood test (gFOBT)

These tests are based on guaiac which is a tree extract that reacts with haem-part of haemoglobin in faeces, but a risk of false positive results from non-human haemoglobin exists. Also vegetable peroxidases can interfere with the reaction. Hence, dietary restrictions omitting red meat, fresh fruit, vitamin C, iron preparations, ASA and NSAIDS were initially mandated, but are being abandoned, since their effect on the outcome is moderate while they negatively affect compliance. The test kit requires two samples from each of three consecutive stools. The result is a qualitative measurement of a methylene blue dye and there are different algorithms used in different screening programmes to define test positivity. The test can be rehydrated, which has proven to improve sensitivity, but also to decrease the positive predictive value of the test. Specificity differs in studies within a range of 90-98 % specificity for CRC and 91-99 % for adenomas, while the sensitivity range is 31-64 % for CRC and 14-41 % for adenomas⁹⁵.

In the 1990s, results from three large randomised trials in Nottingham, Funen and Minnesota were published, demonstrating a mortality reduction in colorectal cancer following screening with gFOBT. A fourth, Swedish trial was also initiated in the 1990s, however results were not reported until 2008. The Nottingham trial and Funen trials both compared biennial screening with gFOBT followed by colonoscopy when positive, to non-screening, and demonstrated a CRC mortality reduction in the screening group with 15 % and 18 % respectively^{96,97}. The Minnesota trial had three arms, comparing annual or biennial screening with gFOBT to a control group without screening. In the first 13-year follow-up a 33 % reduction of mortality in CRC was observed only in the annual screening group, compared to the controls and the biennial group, in which no statistically significant reduction in mortality was seen⁹⁸. However, after 18 years of follow-up, a cumulative mortality reduction in CRC of 21 % could be demonstrated in the biennial group compared to the control arm⁹⁹. In all the trials a shift towards earlier tumour stages were noted in the screening groups. The Swedish randomised trial comparing a gFOBT screening cohort to a non-screened population reported similar results with a 16 % reduction in mortality from CRC in the screening group¹⁰⁰. The age span of screening was heterogeneous between the trials including individuals 45-74 years in the Nottingham and Funen trial, 50-80 years in the Minnesota trial and 60-64 years in the Swedish trial.

Faecal immunochemical tests (FIT)

These kinds of tests use antibodies raised against the globin part of haemoglobin and are specific for human blood. One faecal sample is enough and the measurement is quantitative. Sensitivity is determined by the selected cut-off concentration of haemoglobin. Sensitivity for CRC is 82-92 % and for adenomas 30-34 % while specificity is 90-97 % for CRC and 91-98 % for adenomas at the recommended cut-off level of 100 ng/ml⁹⁵. The compliance in FIT is higher than after FOBT¹⁰¹. One of the reasons for this is probably that only one sample is required, compared three samples in gFOBT.

Stool DNA

This technique investigates the presence of abnormal DNA methylation products in faeces. Thus, stool DNA tests have the potential to detect a neoplasm in the absence of bleeding. Meta-analyses suggest that stool DNA markers have a higher sensitivity for detection of CRC (52-91 %) and adenomas compared to one-time FOBT (13-35 %) ¹⁰². However, there is no set standard for the number and type of markers that should be included in the test to reach the required sensitivity, or which testing interval that should be recommended. Also, cost is a drawback compared to other screening methods and stool DNA is currently not recommended in population based screening programs.

Factors influencing the outcome of faecal screening tests

Age

With increasing age the uptake, *i.e.* the proportion of individuals completing the test, positivity and cancer detection rates and the positive predictive value in screening with gFOBT increase¹⁰³. The positive predictive value and faecal haemoglobin concentrations increase with age in screening with FIT^{104,105}.

Gender

Men have a higher incidence of distal cancer and a higher risk of advanced cancer findings at the screening colonoscopy^{106,107}. Furthermore, the cancer detection and positivity rates and positive predictive value using gFOBT are higher in men, as are the positivity rates and the faecal haemoglobin concentrations using FIT¹⁰⁴⁻¹⁰⁸.

The uptake, irrespective of gFOBT or FIT is higher in women, who reach the same levels of CRC incidence and mortality seen in men, but 4 to 8 years later^{109,110}. Despite this the rate of interval cancer, *i.e.* cancers that are diagnosed after a negative screening test but in the interval before the next scheduled test, is higher in women¹⁰⁸.

Compliance

In most population based screening programmes with FOBT the overall uptake is below 60 %, even though its higher with FIT than with gFOBT¹⁰⁹. In the randomised sigmoidoscopy trials the participation rates in the intervention groups ranged from 58-87 %¹¹¹.

In groups with low socio-economic status, the uptake in gFOBT, the uptake of colonoscopy in men with positive gFOBT, and furthermore the positive predictive value for cancer of gFOBT is reduced ¹⁰³. A relationship between increasing social deprivation and higher levels of faecal haemoglobin concentrations has also been demonstrated using FIT ¹⁰¹.

Regarding gender differences, gFOBT and FIT both detect male cancer to a higher extent than female. This could partly be explained by the larger proportion of more distal, thus more bleeding tumours in the male population. Despite the higher uptake in women and the fact that women reach the same incidence and mortality of the disease later than men, interval cancers are more frequently seen in women. These differences imply that a gender based differentiation in population based screening programmes could be considered, using a lower FIT cut-off value for women and a later age-interval for screening in women. How to reach the socially deprived groups and to increase the overall uptake in screening programs and furthermore deciding which ages to include, which screening interval is optimal and which method is the most cost-effective are other important issues to consider henceforth.

Flexible sigmoidoscopy

Four large randomised trials have reported on the effect on CRC incidence and mortality using sigmoidoscopy as the primary means of screening. A multicentre randomised trial in the UK comparing once-only flexible sigmoidoscopy to no intervention in individuals 55-64 years of age, demonstrated a reduction in CRC incidence and mortality of over 30 % and 40 % respectively in those who underwent screening (per-protocol analysis) ¹¹². Almost identical results regarding incidence and mortality was demonstrated in the per-protocol arm in an Italian multicentre randomised study with a protocol similar to the UK study ¹¹³. In both trials eligible individuals prior to inclusion answered a question on whether they would accept an offer of screening. This procedure in order to increase statistical power could however also be a potential source of self-selection bias. An American trial used data from the multicentre Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. The colorectal cancer part of the trial compared no intervention to sigmoidoscopy at two occasions, 3 or 5 years apart, and demonstrated a 21 % reduction of CRC incidence in the sigmoidoscopy group compared to the control group. The reduction in incidence was significant for both distal (29 %) and proximal (14 %) cancer. The overall 26 % reduction in CRC mortality was represented by a 50 % mortality reduction in patients with distal cancer, while no significant reduction in proximal cancer was seen compared to the control group ¹¹⁴. Opposite to results from the American trial no statistically significant incidence reduction could be demonstrated for cancer in the proximal colon in the UK and Italian trials. Finally, a Norwegian trial comparing flexible sigmoidoscopy ± FOBT to non-screening in 56.000 participants aged 55-64 years reported no difference in 7-year cumulative CRC incidence between the groups. However, for those actually screened (per-protocol group) CRC mortality was reduced by 59 % overall, and by 76 % in patients with distal cancer compared to controls ¹¹⁵. In the intention-to-screen group, CRC mortality was reduced by 27 % overall, and by 37 % in distal cancer, but this was not statistically significant. One possible explanation to this, according to the authors, would be that the time from precursor lesion to cancer is longer than expected, therefore not being caught by the minimum of 5-

year mortality follow-up. However, after a 20-year follow-up in the Nottingham FOBT trial, with removal of hundreds of adenomas, there was no significant difference in CRC incidence between the intervention and control arm ¹¹⁶. This is interesting and not in line with the results from the UK, Italian and US sigmoidoscopy trials, but in concordance with the Norwegian trial where no difference in CRC incidence was seen between the screened and non-screened group. Either the adenoma-cancer pathway is not as strong as presumed or it's the opposite: we don't remove enough of adenomas to have an effect on CRC incidence. Thus, the effect on mortality, for those undergoing sigmoidoscopy seems unquestionable, at least for distal cancer, but the effect on CRC incidence and the benefit of adenoma-removal needs further evaluation.

Optimal age of sigmoidoscopy screening

According to a report for the British National Health System (NHS) an optimal age interval for sigmoidoscopy screening could be theoretically modelled. Screening at the age of 55 with sigmoidoscopy generated the greatest gain in quality adjusted life years (QALYs), but the greatest reduction in CRC incidence and mortality was seen for screening with sigmoidoscopy at the age of 64. Screening with sigmoidoscopy at age 55 followed by biennial FIT until age 74 was considered the overall most effective strategy, taking into account the reduction in CRC incidence, mortality and costs ¹¹⁷.

Colonoscopy

Colonoscopy as a primary means of screening is widely used for example in the U.S., however no randomised trials have been performed comparing colonoscopy to non-intervention regarding the incidence and mortality of CRC. Observational studies comparing colonoscopy to no intervention demonstrate a 69 % and 68 % reduction of CRC incidence and mortality respectively in summary estimates from a recent meta-analysis by Brenner *et al.*, 2014 ¹¹¹.

The NordICC trial, currently recruiting, is a multicentre randomised trial, investigating the effect of colonoscopy screening on CRC incidence and mortality. Once-only colonoscopy screening with removal of all detected lesions is compared to no screening in individuals 55-64 years ¹¹⁸. The Swedish SCREESCO trial is a three armed study launched in 2014 aiming to include 200.000 individuals at the age of 59-62 years; 20.000 to once-only colonoscopy, 60.000 to faecal immunological test (FIT) (year 1 and 3) followed by colonoscopy if positive, and 120.000 as controls. CRC incidence and mortality are the primary outcome measures ¹¹⁹.

Quality indicators of colonoscopy

Adenoma detection rate and caecal intubation rate are two important quality indicators of colonoscopy, as are perforation and post polypectomy bleeding in terms of complications. According to the recommendations of the American Society for Gastrointestinal Endoscopy (2015) the performance targets in CRC screening colonoscopies are: photo-documented caecal intubation rate $\geq 95\%$, adenoma detection rate $\geq 25\%$, perforation $< 1/1000$, and post-polypectomy bleeding $< 10/1000$ ¹²⁰.

Interval cancers are defined as cancers that are diagnosed after a negative screening test but in the interval before the next scheduled test. An interval cancer represents either a false negative

screening test or a new cancer case and reflects the sensitivity and quality of the screening test. There is some evidence that a high adenoma detection rate ($\geq 20\%$) of the individual endoscopist is correlated with a lower risk of interval cancer¹²¹.

Current screening recommendations

Since 2003 the European Union recommends screening with FOBT in men and women aged 50 to 74 years¹²². The recommendation states that: “The screening tests...can only be offered on a population basis in organised screening programmes with quality assurance at all levels, if good information about benefits and risks, adequate resources for screening, follow-up with complementary diagnostic procedures and, if necessary, treatment of those with a positive screening test are available.” However, within the EU the implementation of the recommendation is divergent regarding the extent of implementation, the choice of screening method and whether the programmes are population based or not¹²³.

The Swedish Board of Health and Welfare recommends that men and women between 60 and 74 years should be offered screening for CRC with FOBT¹²⁴. Currently only the Stockholm/Gotland region in Sweden offers population based biennial screening for CRC with gFOBT, at the age of 60-69 years. This centrally administered programme started in 2008, successively including two birth cohorts annually, with inclusion of all cohorts by 2014. Test-kits are mailed to the screening individuals, including a remainder after 8 weeks in case of no return. Positive tests ($\geq 1/3$ test cards) are followed by a referral for colonoscopy within two weeks at designated centres and all data are prospectively collected in a register. Parallel to this ongoing screening programme the national SCREESCO study was launched in 2014, in which the Stockholm/Gotland region is not participating. This three-armed study compares colonoscopy once-only to FIT (year one and three) and to a control group. CRC incidence and mortality is the primary outcome measure, and the aim is to establish recommendations on how to model a future national population based screening program for CRC.

In the United States, colonoscopy is widely used as a primary means of screening, however not in population based programmes. The American College of Gastroenterology (ACG) has chosen a different CRC screening strategy compared to Europe, dividing CRC screening into prevention and detection tests. Colonoscopy every 10 years beginning at the age of 50 is recommended as the primary prevention test and annual FIT as the primary detection test according to ACG guidelines¹²⁵.

AIMS OF THE THESIS

Overall aim

To individualise treatment for patients with early CRC and to contribute to the goal of offering a treatment that minimises complications, morbidity and mortality while ensuring a fully adequate oncological outcome.

Specific aims

Paper I

To assess the correlation between surgical intervention, age and long term survival in patients undergoing surgery for stage I rectal cancer. To see whether local excision could provide long term survival equivalent to TME surgery in patients ≥ 80 years of age.

Paper II

To assess risk factors for lymph node metastases in T1 and T2 rectal cancer.

Paper III

To compare patients with screening and non-screening detected CRC regarding staging, MDT-assessment and treatment.

Paper IV

To assess the collected burden of complications and mortality following colonoscopy and surgery for adenomas and CRC in patients with a positive screening FOBT.

PATIENTS AND METHODS

The Swedish Colorectal Cancer Registry (SCRCR)

This national quality registry was started in 1995 and is prospectively and continuously collecting data on all patients with adenocarcinomas of the colon and rectum, covering > 98 % of all CRC cases in Sweden with a demonstrated high validity ^{2,3,126}. Rectal cancer is defined as an adenocarcinoma within 15 cm from the anal verge. The registry is used for national quality audits and research and contains detailed information on preoperative work-up, clinical staging (cTNM) and the surgical procedure and postoperative complications including 5-year follow-up of recurrence and death. Also included is the histopathology report with staging (pTNM) and information on neoadjuvant and adjuvant treatment. The SCRCR is linked to the Swedish Cancer Register and the Cause of Death Register.

The Screening Register in the Stockholm/Gotland screening programme

All data from the population based screening programme in the Stockholm-Gotland region are prospectively collected in a register which contains detailed information on the screening process and the colonoscopy procedure, including data on intra-procedure complications and performance quality parameters such as caecal intubation rate (with photo documentation) and adenoma detection. Diagnoses from the histopathological examinations of excised specimens are also registered.

Registers held by the Board of Health and Welfare

The National Board of Health and Welfare is a Swedish government agency under the Ministry of Health and Social Affairs. The National Board of Health and Welfare is responsible for several registers, some of which are used in Paper I-IV:

- **The Swedish National Patient Register (NPR):** The Register has been collecting information since the 1960s. In 1984 participation was decided mandatory and registration of ICD-codes is linked to economical reimbursement systems for the hospitals.

The Inpatient register (IPR): Is a part of the NPR. Since 1987 all in-patient care in Sweden is included and ≥ 99 % of all hospital discharges are registered in the IPR, which has been validated showing up to 95 % accuracy of diagnoses registered ¹²⁷.

The Outpatient Register: Is also a part of the NPR. Outpatient surgery is included since 1997 and since 2001 outpatient visits from both private and public health providers are included.

- **The Cause of Death Register:** Data is available since 1961. The cause of death is derived from individual death certificates. Since the frequency of autopsy is only around 20 %, the reliability of the cause of death is depending on how accurately the probable cause of death is reported. The overall accuracy of death certificates is 77 % and is higher in younger individuals, after rapidly progressive disease or malignant disease and after trauma ^{128,129}.
- **The Cancer Register:** All health care providers in Sweden are bound by law to report all cases of cancer to this register.

Paper I

All patients in Sweden undergoing surgery for stage I (T1-2N0M0) rectal cancer January 1, 1995 - December 31, 2006 were included in the analysis. Relative and overall survival and risk factors for mortality within 5 years after surgery were calculated for the whole cohort and in the age groups < 80 and \geq 80 years respectively. Local recurrence rates, the use of preoperative radiotherapy, comorbidity as defined by the American Society of Anaesthesiologists (ASA) physical status classification and age were assessed in relation to surgical intervention.

Information of the ASA classification was obtained through a separate sample, including a random selection of 400 patients (equally distributed between local excision and anterior resection/APE surgery) from 60 hospitals in the country. The hospitals were asked to contribute with the ASA classification as noted in the medical records at the time of surgery.

In order to sub-classify surgical techniques in the local excision technique group, data from the National Patient Registry regarding procedure codes were extracted and merged with the original cohort data.

Paper II

All patients in Sweden undergoing abdominal surgery for rectal cancer January 1, 2007 – December 31, 2010, without (neo)adjuvant treatment, and with histopathologically confirmed radical resections of pT1-T2 tumours were included.

Evaluation of possible predictors of lymph node metastases included the following factors available in the SRCR: tumour stage, level of submucosal infiltration (sm-level), tumour differentiation, mucinous tumour type, blood vessel and perineural infiltration, tumour location in the rectum (cm from anal verge), age and gender.

Paper III

The study included all individuals with a positive FOBT in the Stockholm/Gotland screening programme January 1, 2008 - December 31, 2012. From this cohort, those with a histopathologically verified CRC were further analysed. For comparison, all patients with non-screening detected CRC in Sweden, diagnosed during the same period of time and matched by age, were included. The groups were compared regarding tumour stage, preoperative staging, MDT-assessment, surgical and oncological treatment.

Paper IV

All patients in the Stockholm/Gotland screening programme, with one positive FOBT followed by a colonoscopy performed January 1, 2008 until June 30, 2012 were included. The 30-day mortality and complications, defined as events requiring over-night hospital care within 30 days after colonoscopy or surgery for adenomas or CRC, were analysed and all adverse events deviating from a normal postoperative course were registered after revision of hospital charts. In patients with multiple complications, the most severe one was registered according to the Clavien-Dindo classification of surgical complications¹³⁰.

Statistical analyses paper I-IV

Paper I

Kaplan-Meier estimates were used to calculate 5-year overall survival rates. Relative survival was calculated using the Hakulinen method. Hazard ratios (HR) for death were calculated using Cox proportional hazards regression model. Mann-Whitney U test and Chi2 test were used to compare the distribution of ASA classes between two groups of surgical interventions. Kruskal-Wallis test was used for comparison of median ages between different groups of surgical interventions. P-values < 0.05 were considered statistically significant.

Paper II

The risk of lymph node metastases, expressed as odds ratios (OR), was calculated using uni- and multivariate logistic regression analyses.

An index for predicting the risk of lymph node metastases was constructed including variables with a statistically significant risk for lymph node metastases according to the multivariate logistic regression analyses. The predicted probability estimating the aggregated risk of lymph node metastases was based on the intercept and estimate of the multivariate analyses.

Paper III and IV

Pearson Chi2 test and Fisher's exact test were used to determine significant differences in proportions. P-values < 0.05 were considered statistically significant.

Statistical analyses were performed using the Statistica Release 8 (Statsoft, Tulsa, USA) and Stata 12.0 (StataCorp, 4905 Lakeway Drive, Collage Station, Texas 77845, USA).

Ethical permission

All studies were approved by the Regional Ethical Review Board in Stockholm.

RESULTS

Paper I

A total of 3964 patients underwent surgery for stage I rectal cancer. Table 6 shows the distribution of surgical interventions, preoperative radiotherapy and 5-year local recurrence rates.

Table 6. Surgical interventions, preoperative radiotherapy and local recurrence rates in patients undergoing surgery for stage I rectal cancer.

	Type of surgery (n)	Preoperative Radiotherapy (%)	Local recurrence (%)
Anterior resection	1947 (52%)	48	2.2
Abdominoperineal Resection	982 (27%)	68	3.5
Hartmann's procedure	235 (7%)	35	7.2
Local excision	448 (12%)	2	11.2

Unspecified type of surgery, n= 64, excluded

A poor survival was demonstrated in patients undergoing local excision and Hartmann's procedure compared to patients undergoing AR or APR. In the age group ≥ 80 years this difference was even more pronounced as shown in table 7.

Table 7. Total and relative 5-year survival rates after surgery for stage I rectal cancer.

	Total Survival All Ages	95 % CI	Relative Survival <80 y	95 % CI	Relative Survival ≥ 80 y	95 % CI
AR	0.80	(0.82-0.78)	0.94	(0.92-0.96)	0.99	(0.88-1.09)
APE	0.75	(0.72-0.77)	0.88	(0.85-0.92)	0.95	(0.80-1.10)
Hartmann's Procedure	0.57	(0.50-0.63)	0.72	(0.62-0.82)	0.91	(0.71-1.12)
Local excision	0.62	(0.57-0.66)	0.84	(0.77-0.90)	0.74	(0.59-0.89)

AR (anterior resection), APE (abdominoperineal excision).

The median age was 5 years higher in patients undergoing local excision compared to those undergoing anterior resection ($p < 0.001$). In patients ≥ 80 years the corresponding difference was 2 years ($p < 0.001$). The ASA classification of physical status was higher in the local excision group compared to the AR/APE group ($p < 0.005$).

Statistically significant risk factors for mortality within five years after surgery as seen in the multivariate analysis were: APE, $HR = 1.22$ (1.03-1.45), Hartmann's procedure, $HR = 1.61$ (1.28-2.02), local excision, $HR = 1.58$ (1.30-1.91), increasing age $HR = 1.06$ (1.06-1.07), male gender 1.70 (1.48-1.95).

Among patients ≥ 80 years of age local excision $HR= 1.55$ (1.17-2.05), male gender $HR= 1.59$ (1.27-1.99) and age $HR= 1.07$ (1.04-1.11) were statistically significant risk factors for mortality.

In the local excision group further sub-division of the surgical procedures was possible in 363 patients: TEMS $n= 98$ (22 %), transanal excision, $n= 210$ (47 %) and endoscopic resection, $n= 55$ (12 %). Multivariate analysis with sub-division of the local excision group showed the following hazard ratios for mortality within 5 years after surgery: endoscopic resection, $HR= 1.79$ (1.17-2.74), TEM, $HR= 1.69$ (1.20-2.37), transanal excision, $HR= 1.62$ (1.27-2.09), missing data 1.17 (0.76-1.81).

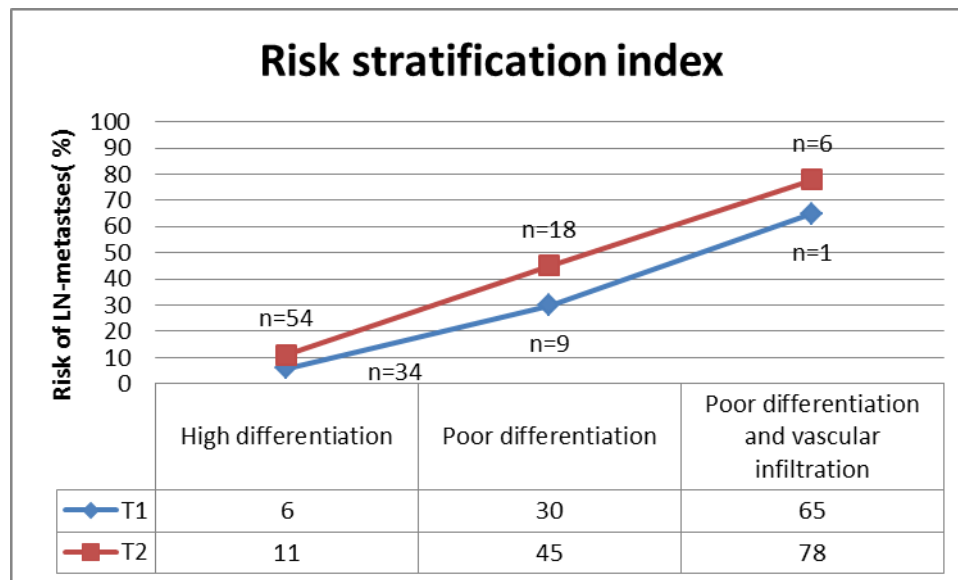
Paper II

In paper II, 205 patients with T1 and 472 patients with T2 disease were identified, and the overall proportion of patients with lymph node metastases were 12 % and 22 % in patients with T1 and T2 tumours respectively.

The multivariate logistic regression analyses identified the following risk factors for lymph node metastases: T2 tumour stage, $OR= 1.97$ (1.19-3.25), poor differentiation, $OR= 6.47$ (2.71-15.4), vascular infiltration, $OR= 4.34$ (2.46-7.65).

Stratification of risk depending on the number of risk factors added is shown in figure 2. The risk index shown here is a revised and corrected version of the index published in paper II. The revision of does not affect the risk of lymph node metastases.

Figure 2. Risk of lymph node metastases in T1 and T2 tumours.



Paper III

Among the nearly 206.000 individuals receiving a test kit, compliance was 64 %. The positivity rate (positive FOBT/ performed tests) was 3.5 % and the positive predictive value of colonoscopy, *i.e.* histopathologically confirmed CRC in patients undergoing colonoscopy after a positive FOBT was 6 %. Staging of the primary tumour and metastases, and MDT assessments were more complete in patients with screening detected cancer compared to those with non-screening detected cancer ($p < 0.0001$). Within both groups, among patients with endoscopically resected cancer, staging and preoperative MDT assessment was less complete than among patients with surgically resected cancer ($p < 0.001$).

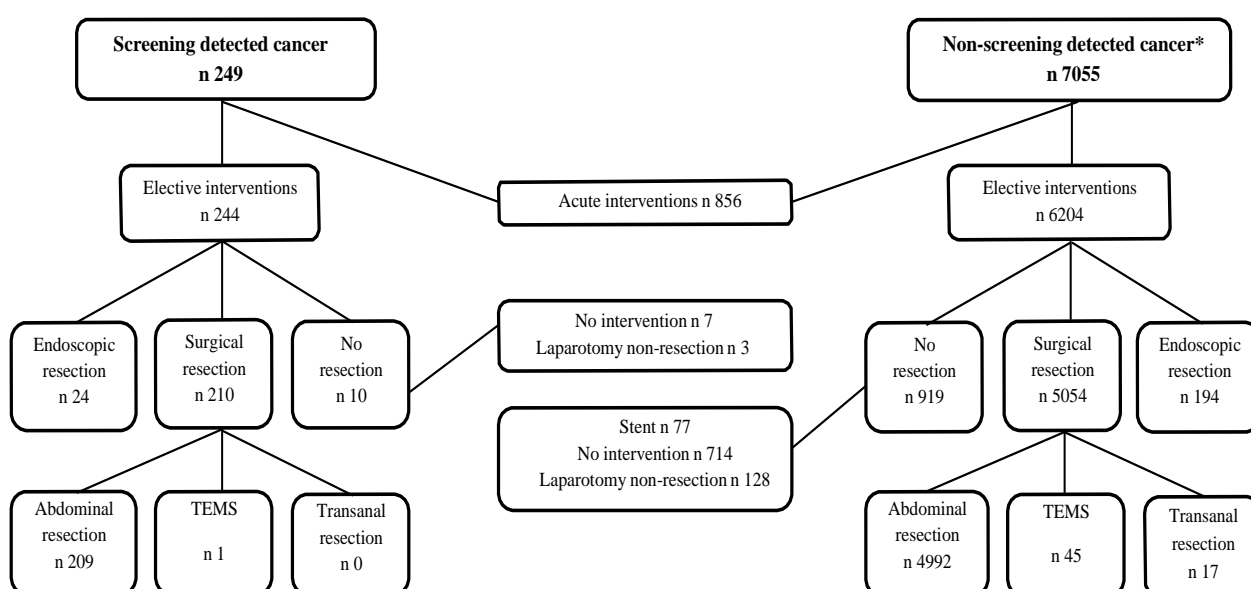
A higher proportion of stage I disease, 41 % *vs.* 15 % (pTNM) ($p < 0.001$), a larger proportion of colon cancer, 72 % *vs.* 62 % ($p < 0.05$) and fewer acute interventions 2 % *vs.* 12 % ($p < 0.001$) were seen in the screening, compared to the non-screening group.

Of patients undergoing elective surgical resection, 99.5 % and 99 % in the screening and non-screening group respectively underwent abdominal resection surgery (*Fig 3*).

In patients electively treated for rectal cancer in (cTNM) stage I disease, there was no difference between the screening and non-screening groups regarding the use of local excision techniques ($p = 1.0$). In the screening group 23 % of patients had stage I disease and 6 % of these were treated with local excision. The corresponding numbers in the non-screening group were 6 % stage I disease and 9 % treated with local excision.

Neoadjuvant (C)RT was given to 68 % and 76 % of patients with rectal cancer in the screening and non-screening groups respectively ($p = 0.14$). Regarding adjuvant chemotherapy in (pTNM) stage II and III, no statistically significant difference was seen between the groups ($p = 0.15$).

Figure 3. Treatment in patients with screening and non-screening detected CRC.



* Excluded, n= 37: unspecified operation (n= 16), appendectomy (n= 9), missing (n= 12)

Paper IV

Subsequent to a positive gFOBT in the screening programme 2984 individuals underwent a colonoscopy. Of these, 37 and 155 patients underwent surgery for adenomas and CRC respectively. After colonoscopy the incidence of post-polypectomy bleeding was 14/1000. Perforation occurred in 1/1000 after diagnostic procedures and 2.5 /1000 after therapeutic procedures. Post-polypectomy syndrome occurred in one patient. The total complication rate after colonoscopy was 1 %. One patient died within 30 days after colonoscopy, but without relation to the colonoscopy-procedure. In the adenoma surgery group the complication rate was 27 % and the rate of anastomotic leakage was 13 %. In the cancer surgery group complication and anastomotic leakage rates were 50 % and 12 % respectively. There was no 30-day mortality after surgery for adenomas or cancer. No statistically significant correlation regarding complications was seen in relation to tumour stage ($p= 0.8$), or when comparing prevalent and incident screening rounds ($p= 0.4$).

DISCUSSION

Screening for colorectal cancer

Screening for CRC enables detection and removal of precursor lesions, *i.e.* adenomas, and detection of cancer at an early stage, which is the key to reducing CRC mortality, since survival in CRC is dependent on tumour stage. In randomized trials using gFOBT, a 16 % reduction in CRC mortality has been demonstrated, and also detection of cancer at an earlier stage in screening compared to control groups ¹³¹. Later RCTs assessing screening sigmoidoscopy have demonstrated an incidence reduction in distal CRC of 31 % and 42 % in the intention to screen and per protocol analysis respectively, with corresponding numbers of 41 % and 61 % in the reduction of distal CRC mortality ¹¹¹.

In paper III follow-up time did not allow for assessment of long term survival, but in line with the randomized trials assessing gFOBT, screening detected cancer was found at an earlier stage, both cTNM and pTNM stage, compared to non-screening detected cancer. Emergency interventions were fewer in the screening compared to the non-screening group (2 % *vs.* 12 %), which is likely to impact survival since previous studies have demonstrated that emergency intervention is a risk factor for increased short term mortality and reduced long term survival ¹³².

However for a screening programme to be efficient, not only reduction in CRC mortality is needed but also adherence to the programme. In paper III uptake with gFOBT was 64 %, which is high compared to other studies and considering that compliance is generally lower with gFOBT compared to FIT. For example the Scottish screening programme demonstrated an uptake of 54 % with gFOBT and 59 % with FIT ¹⁰⁹. In paper III, 88 % of individuals with a positive FOBT underwent the recommended colonoscopy indicating that individuals participating in the programme are motivated to complete investigations following a positive test result. In the UK and Italian sigmoidoscopy trials compliance was 71 % and 58 % respectively, however inclusion was made from individuals indicating an interest to attend screening, thereby inducing possible self-selection bias ^{112,113}. The Norwegian sigmoidoscopy trial was population based, reporting an attendance rate to sigmoidoscopy of 65 % indicating that high compliance could be achieved to an invasive procedure without previous selection of participants ¹¹⁵. How compliance would be in a fully expanded population based program using sigmoidoscopy or colonoscopy outside a trial situation is not known.

Complications and overtreatment are two other important issues of screening programmes. Complications after colonoscopies and cancer surgery are well documented, but very few studies have tried to assess the collected burden of complications that arise as a result of a positive FOBT. In paper IV, complications after colonoscopy, surgery for adenomas and surgery for CRC were evaluated. Total complication rates of 27 % and 50 % after adenoma and CRC surgery respectively were demonstrated. The rates of anastomotic leakage were 13 % and 12 % in the adenoma and CRC surgery groups respectively. The rates of post-

polypectomy bleeding and perforation were 14/1000 and 2.5/1000 respectively, reported per patient and not per polypectomy. Compared to a previous study by Kewenter *et al.* assessing the collected complications after screening-induced interventions in the randomized Gothenburg FOBT-trial in the 90s, the complication rates presented in paper IV are high. Kewenter *et al.* reported a total complication rate of 13 % after surgery for CRC and benign findings¹³³. However, many present studies report total complication rates of 50 % after CRC surgery, but usually lower rates of anastomotic leakage than those presented in paper III are reported^{38,42,134}. The reasons for this could be that the definition of anastomotic leakage is not uniform, and that reporting, validity of reported data, and the possibility of scrutinizing medical charts may vary. Robinson *et al.* reporting from the Nottingham randomized trial on gFOBT screening reported a perforation rate of 3/1000, and the study by Kewenter *et al.* presented a post-polypectomy perforation rate of 8/1000 which is higher than in paper IV^{133,135}.

Reduction of mortality in CRC is the primary outcome measure when evaluating screening and such a precise measure is difficult to implement when assessing the impact of overall complications generated by screening. This makes it hard to compare net effects in terms of mortality reduction contra risks as long as the magnitude of the complications doesn't counterbalance the mortality reduction in CRC. Putting the results of paper IV in relation to other studies and quality guidelines, the complication rates in paper IV are judged to be within acceptable limits.

The idea of the adenoma-carcinoma pathway is generally accepted and hence removal of screening detected adenomas is adequate in order to reduce CRC incidence and mortality^{93,94}. However, not all precursor lesions will transform into malignant lesions. Removal of adenomas with low grade dysplasia, where colonoscopy or subsequent surgery leads to complications is a problem of overtreatment. In paper IV, the total number of complications after adenoma surgery was small, as was the number of patients undergoing surgery for adenomas. Thus on a cohort level, overtreatment of adenomas is not a problem, but for the individual patient and surgeon complications after "unnecessary" surgery are problematic.

In paper III, there were no statistically significant differences between the screening and non-screening groups regarding the extent of surgical or oncological treatment, hence neither over-, nor under-treatment could be detected in the screening compared to the non-screening group.

The implementation of population based screening programmes for CRC will generate a higher proportion of early stage cancer. Consequently, for these patients with early stage cancer, treatment options minimising morbidity are of importance. In this perspective local excision techniques and non-surgical treatment will come in to focus.

Early rectal cancer

The different treatment options in early rectal cancer have gained more attention than those of early colon cancer. This is due to anatomical differences between the colon and rectum, which will impact treatment and results. The envelope of the mesorectum allows for full thickness local excision techniques of early tumours below the peritoneal reflection. This is not possible in the colon where a corresponding procedure would lead to a perforation into the abdominal cavity. Furthermore, the functional consequences of an AR or APE compared to organ sparing techniques in the rectum are apparent, whereas the corresponding functional disadvantages of open surgery compared to minimally invasive techniques in colon surgery are less pronounced.

The TME-technique has set a reference point for survival and local recurrence rates in rectal cancer. However, regarding morbidity, mortality, functional outcome, organ preservation and patient preference in early rectal cancer treatment possibilities other than AR or APE, *i.e.* local excision techniques are of interest. Initially, transanal excision was the only alternative in local excision of rectal cancer, but with technical advances TEMS is now the surgical method of choice. In endoscopy, the ESD technique allows for en-bloc resections of larger lesions than previously. Furthermore the prospect of complete response after neoadjuvant CRT has emerged as yet another alternative in the treatment of early rectal cancer.

However, all techniques of local excision face the same central dilemma regarding lymph nodes: radiology cannot (yet) predict the presence of lymph node metastases with a specificity of more than around 70 % and local excision techniques cannot remove the mesentery and possible lymph node metastases⁶. The non-resected nodes account for the problem of high local recurrence rates after local excision surgery. To some extent also non-radical resections contribute to higher local recurrence rates, especially using transanal excision, but with the introduction of TEMS, non-radical resections are no longer a major issue^{63,89}.

One way of dealing with the problem is to consider local excision with TEMS as a "macro-biopsy". If histopathology would reveal the presence of adverse features increasing the risk of lymph node metastases, additional treatment with AR or APE would be recommended. In paper II, risk factors for lymph node metastases were assessed, demonstrating T2 stage, poor differentiation and vascular infiltration as statistically significant risk factors for lymph node metastases. These factors are also identified by other studies along with a number of other risk factors such as tumour depth of invasion, lymphatic invasion and tumour budding^{71,72}.

Since long the correlation between intramural invasion and an increasing risk of lymph node metastases has been demonstrated^{66,67}. However, as demonstrated in paper II, not only stage, but the combination of different risk factors determines the overall risk of lymph node metastases. In paper II, the risk ranges from 6-65 % in T tumours and from 11-78 % in T2 tumours. Thus, a low-risk T2 tumour could have a smaller risk of lymph node metastases than a high-risk T1 tumour. However general recommendations of using local excision for only T1sm1 tumours is not taking into account the differentiation of risk depending on the number of added risk factors⁷⁸. Different studies have constructed other risk stratification models but these are all theoretical models and how to implement the results in clinical practice needs further discussion^{68,136,137}. If using a large population based material not flawed by missing data, based on meticulous histopathological examinations and with future possible biomarkers in-

cluded, a validated, clinically relevant risk index assessing the risk of lymph node metastases after local excision should be possible to construct.

Regarding the issue of salvage surgery, *i.e.* abdominal resection surgery in case of local recurrence after local excision of rectal cancer, studies have demonstrated 3 and 5-year survival rates of 53-58% and distant metastases in 16-39 % of cases ^{138,139}. However, in immediate salvage surgery, meaning abdominal resection surgery within a month after TEMS where histopathology has revealed adverse features, long term survival have been reported as equal to that after primary TME surgery ¹⁴⁰. The procedure of immediate salvage surgery is currently recommended in case of adverse features after local excision of rectal cancer, according to the European Society for Medical Oncology Guidelines for management of rectal cancer ⁷⁸.

In paper I a local recurrence rate of 11.2 % was seen after local excision compared to rates of 2.2 % and 3.5 % after AR and APE respectively. Furthermore, 5-year relative survival after local excision (81 %) was poor in all ages compared to AR (95 %) and APR (89 %), and this difference was even more pronounced in patients ≥ 80 years. In concordance with our findings in paper I, numerous trials have demonstrated higher local recurrence rates after local excision compared to TME surgery whereas, opposite to the findings in paper I, no difference in long term survival has been demonstrated ⁶³. In paper I, the poor survival found in patients undergoing local excision could be due to a selection of old patients with a high comorbidity. The local excision group was further sub-classified to assess 5-year relative survival of patients undergoing resection with TEMS, transanal excision or endoscopic resection. The results were not in favour of the TEMS (75 %) group compared to patients undergoing transanal (82 %) or endoscopic resection (76 %). From available data, the reasons for this are not clear.

Included in the term local excision are endoscopic resections. Due to several reasons endoscopic resections cannot however presently be regarded as a fully equivalent alternative to TEMS in case of rectal cancer. The knowledge of how to use the ESD technique for resection of rectal lesions is still developing. Even if so called en-bloc resection rates, *i.e.* resection of the tumour in one piece, are higher than with traditional endoscopic resection techniques using piecemeal resection, en-bloc resection are performed in 90-97 %, and complete R0 resections only in 80-97 % of cases ^{61,141}. Furthermore, the issue of lymph node metastases remains the same as in other local excision techniques. No large studies regarding long-term oncological outcome after resection of early rectal cancer comparing ESD to TME surgery have been performed. Finally, as demonstrated in paper III the preoperative staging and MDT-assessment of patients with endoscopically resected, both screening detected and non-screening detected CRC is performed to a smaller extent than in the surgical resection groups. This is also an indication that endoscopy has not yet found its place as a fully adequate option for resection of CRC.

In recent years a lot of interest has arisen around organ preservation and complete response after neoadjuvant therapy with or without additional surgery in case of early rectal cancer. The CRT regimen used in many of the trials assessing complete response is equivalent to the long-course CRT advocated for downstaging of advanced rectal cancer ^{78,87-90}. This way of using the most intense CRT for early rectal cancer is not in line with traditional reasoning around benefits and side effects of neoadjuvant therapy, at least not in how it has been re-

flected in guidelines for early rectal cancer, where recommendations are to proceed to surgery without previous neoadjuvant therapy. In case of success, *i.e.* complete clinical response, the goal of organ preservation is achieved, and the cost for the individual patient in terms of negative side effects is probably acceptable. However, in case of no response; a situation requiring additional AR or APE, the patient will not only have the side effects of pelvic surgery itself, but also of heavy CRT.

By combining (C)RT and TEMS the risk of leaving of remaining lymph node metastases decreases due to the neoadjuvant therapy, even if the central problem with the local excision technique and lymph nodes remains. However, if subsequent abdominal resection surgery is needed in case of local failure, the patient will, as in the case of incomplete response, encounter the negative side effects of both CRT and pelvic surgery. In addition, the abdominal resection surgery can be more complicated due to scarring after TEMS.

Looking at time trends in the use of local excision in stage I rectal cancer in Sweden no increase is seen over time. In paper I, 12 % of patients with stage I rectal cancer underwent surgical treatment with local excision in 1995-2006, compared to 9 %, 2007-2010 (paper III). The difference when comparing with the US where 55 % of stage I rectal cancer was treated with local excision in 2010, is interesting. The underlying causes for these differences are not clear⁶⁴.

FUTURE PERSPECTIVES

Further expansion of population based screening for CRC will generate a need of follow-up after screening detected cancer and adenomas. How to allocate nationally equal resources for the consequent need of colonoscopy, even in screening programmes using FOBT, could become a challenge. There is also an interesting issue of compliance when multiple screening programmes are running in a population. A woman in living in Sweden today is invited to attend screening programs for breast cancer, cervical cancer and (if living in the Stockholm-region) colorectal cancer. How will individual compliance be affected by participation in multiple non-synchronised screening programs?

With coming generations of well-informed CRC patients and patient-organisations, the demand for surgical interventions with a low morbidity combined with good functional and aesthetical results in early CRC is likely to increase. The increasing awareness within the surgical society on the issue of function and quality of life after surgery, in combination with the surgical interest in minimally invasive techniques will continue to drive the development and utilisation of laparoscopic, robotic and endoscopic surgery. Currently experimental techniques such as transanal total mesorectal excision and combined endoscopic/laparoscopic procedures will probably be developed and further integrated as possible treatment options^{62,142}. Furthermore, radiological advances increasing the accuracy in predicting lymph node metastases would facilitate the selection of patients with tumours suitable for local excision techniques.

The issue of complete tumour response after neoadjuvant therapy has created the possibility of a non-surgical treatment with a curative intent. Also the combination of different neoadjuvant treatment modalities and local excision, *i.e.* TEMS, is gaining attention, with interesting results from ongoing trials to be awaited.

The idea of heavy chemoradiotherapy in early rectal cancer is challenging, since it puts aside the current perception of the risk-benefit ratio of neoadjuvant therapy in early stage disease. The aim of individualised treatment minimising the negative effects of surgery must not come at the price of non-surgical overtreatment.

CONCLUSIONS

- Patients treated with local excision in stage I rectal cancer had a poor 5-year survival compared to patients undergoing surgery with anterior resection or abdominoperineal excision. This difference was even more pronounced in patients ≥ 80 years of age. There could be a selection of old patients with high comorbidity to surgery with local excision.
- T2 stage, poor differentiation and vascular infiltration were risk factors for lymph node metastases in rectal cancer. There was a differentiation of risk depending on the presence of different risk factors, creating a large span between high and low risk T1 and T2 tumours respectively.
- Staging and MDT-assessments were more frequently performed in patients with screening detected cancer compared to those with non-screening detected cancer. The surgical and oncological treatment did not differ between the groups. Patients with endoscopically resected cancer were not staged and MDT-assessed to the same extent as were those with surgically resected cancer, and in this respect, no difference was seen between the screening and non-screening group.
- After interventions following a positive screening FOBT, overall complication rates were acceptable and mortality low after colonoscopy and surgery for adenomas and cancer. However, the rates of anastomotic leakage were higher than expected after surgery.

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